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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/060,759	01/30/2002	Adam Lerner	701586/50174-DIV	8480

50607 7590 02/05/2007

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EXAMINER	
ANDERSON, JAMES D	
ART UNIT	PAPER NUMBER
1614	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/05/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/060,759	LERNER, ADAM	
	Examiner	Art Unit	
	James D. Anderson	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 December 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7 and 15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *15* is/are allowed.

6)☒ Claim(s) *1-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' arguments, filed 12/18/2006, have been fully considered and are deemed to be persuasive. Rejections and/or objections not reiterated from previous Office Actions are hereby withdrawn. However, upon further consideration the following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Continued Examination Under 37 CFR § 1.114

A request for continued examination under 37 CFR § 1.114, including the fee set forth in 37 CFR § 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR § 1.114, and the fee set forth in 37 CFR § 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR § 1.114. Applicant's submission filed on 12/18/2006 has been entered.

Status of the Claims

Claims 1-7 and 15 are currently pending and are the subject of this Office Action. This is the first Office Action on the merits of the application following a request for continued examination.

Priority

This application is a divisional of copending application 09/423,349, filed November 22, 1999, now U.S. Patent No. 6,399,649, issued Jun. 4, 2002, which claims benefit of PCT

application number PCT/US99/21518, filed September 17, 1999, which claims benefit of provisional application 60/101,721, filed September 24, 1998. Support for the instant claims was found in provisional application no. 60/101,721. As such, the earliest effective U.S. filing date afforded the instant claims has been determined to be 9/24/1998.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-7 are rejected under 35 U.S.C. § 102(b) as being anticipated by Feldman *et al.* (U.S. Patent No. 5,665,754; Issued Sep. 9, 1997) (newly cited art).

Instant claims 1-7 are drawn to a method of administering an inhibitor that specifically inhibits Type 4 cyclic adenosine monophosphate phosphodiesterases (PDE-IV) to a patient having symptoms of chronic lymphocytic leukemia (CLL). It is noted that Applicant envisions administering any and all specific inhibitors of PDE-IV to patients with CLL.

Feldman *et al.* teach of novel pyrrolidine compounds, which are useful for inhibiting the function of Type IV phosphodiesterase (Abstract). These compounds are taught to be useful in treating inflammatory diseases and other diseases involving elevated levels of cytokines (*id.*). Multiple types of inflammatory cells, particularly of lymphoid lineage and myeloid lineage, are found at sites of chronic inflammation (col. 1, lines 13-17). PDE-IV is a major mechanism of cAMP degradation and thus inhibition of PDE-IV can "cause elevation of cAMP in these cells

and suppression of cell activation" (*id.* at lines 46-48). In particular, PDE-IV inhibitors have been shown to inhibit production of TNFα and partially inhibit IL-1β release by monocytes (*id.* at lines 54-56). Thus, chemical compounds which "selectively inhibit PDE-IV would be useful in the treatment of allergic or inflammatory diseases or other diseases associated with excessive or unregulated production of cytokines, such as TNF" (col. 2, lines 58-62). Further, "PDE-IV inhibitors would be useful for treatment of diseases which are associated with elevated cAMP levels or PDE-IV function in a particular target tissue (*id.* at lines 62-64). Pharmaceutical formulations, doses and administration routes are taught at col. 36, line 27 to col. 37, line 49. The inventors of the '754 patent explicitly claim a method of treating a mammal for "inflammatory diseases" (Claim 13) and a method of "inhibiting phosphodiesterase Type IV function in a mammal" (Claim 24) by administering the specific PDE Type IV inhibitors as recited in Claim 1. Thus, if a specific PDE Type IV inhibitor as disclosed in the '754 patent is administered to a mammal having CLL, such administration would read on the claims of the '754 patent. It is noted that the instant claims do not recite any limitations with respect to the structure of the Type IV PDE inhibitor.

Thus, the '754 patent inherently teaches the limitations of the instant claims. It is noted that *In re Best* (195 USPQ 430) and *In re Fitzgerald* (205 USPQ 594) discuss the support of rejections wherein the prior art discloses subject matter, which there is reason to believe inherently includes functions that are newly cited, or is identical to a product instantly claimed. In such a situation the burden is shifted to the applicants to "prove that subject matter to be shown in the prior art does not possess the characteristic relied on" (205 USPQ 594, second column, first full paragraph). There is no requirement that a person of ordinary skill in the art

would have recognized the inherent disclosure at the time of invention, but only that the subject matter is in fact inherent in the prior art reference. *Schering Corp. v. Geneva Pharm. Inc.*, 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003); see also *Toro Co. v. Deere & Co.*, 355 F.3d 1313, 1320, 69 USPQ2d 1584, 1590 (Fed. Cir. 2004) ("[T]he fact that a characteristic is a necessary feature or result of a prior-art embodiment (that is itself sufficiently described and enabled) is enough for inherent anticipation, even if that fact was unknown at the time of the prior invention").

In the instant case, the '754 patent teaches the administration of specific PDE-IV inhibitors to mammals. As such, if the specific compounds taught in the patent are administered to a patient having symptoms of CLL, said symptoms will inherently be reduced as instantly claimed. Just as the instant claims do not recite any limitation with respect to the PDE-IV inhibitor administered to a patient having CLL, claim 24 of the '754 patent does not exclude the administration of the compounds taught in the patent to a patient having CLL.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-7 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Feldman *et al.* (U.S. Patent No. 5,665,754; Issued Sep. 9, 1997) (newly cited art) in view of Tangye *et al.* (Immunol. Cell Biol., 1997, vol. 75, pages 127-135) (newly cited art).

Instant claims 1-7 are drawn to a method of administering an inhibitor that specifically inhibits Type 4 cyclic adenosine monophosphate phosphodiesterases (PDE-IV) to a patient having symptoms of chronic lymphocytic leukemia.

Feldman *et al.* disclose novel pyrrolidine compounds, which are useful for inhibiting the function of Type IV phosphodiesterase (Abstract). These compounds are disclosed to be useful in treating inflammatory diseases and other diseases involving elevated levels of cytokines (*id.*). Multiple types of inflammatory cells, particularly of lymphoid lineage and myeloid lineage, are found at sites of chronic inflammation (col. 1, lines 13-17). Pro-inflammatory mediators, including cytokines such as tumor necrosis factor (TNF) and interleukin-1 (IL-1) are produced by these activated cells (*id.* at lines 17-19). As such, the inventors state that an agent which suppresses the activation of these cells or their production of pro-inflammatory cytokines would be useful in the treatment of diseases involving elevated levels of cytokines (*id.* at lines 20-25). Elevated levels of cAMP in human myeloid and lymphoid lineage cells are associated with the suppression of cell activation (*id.* at lines 42-44). PDE-IV is a major mechanism of cAMP degradation and thus inhibition of PDE-IV can "cause elevation of cAMP in these cells and suppression of cell activation" (*id.* at lines 46-48). In particular, PDE-IV inhibitors have been shown to inhibit production of TNFα and partially inhibit IL-1β release by monocytes (*id.* at lines 54-56). Thus, chemical compounds which "selectively inhibit PDE-IV would be useful in the treatment of allergic or inflammatory diseases or other diseases associated with excessive or unregulated production of cytokines, such as TNF" (col. 2, lines 58-62). Further, "PDE-IV inhibitors would be useful for treatment of diseases which are associated with elevated cAMP

levels or PDE-IV function in a particular target tissue (*id.* at lines 62-64). Pharmaceutical formulation, doses and administration routes are disclosed at col. 36, line 27 to col. 37, line 49.

Tangye *et al.* disclose that human cytokines suppress apoptosis of leukemic B cells and preserve expression of bcl-2 (Abstract). Specifically, the authors disclose that CD5+ B cells from B cell chronic lymphocytic leukemia patients rapidly undergo apoptosis during *in vitro* culture. In contrast, these cells demonstrate enhanced longevity *in vivo*, which suggests that apoptosis-inhibitory factors may be responsible for the accumulation of leukemic cells in B-CLL. In the presence of cytokines (*e.g.* IL-2, IL-6, IL-13 and TNFα), 10-40% more viable cells were detected compared with unstimulated cultures. Enhancement of cell viability and suppression of apoptosis were associated with a delay in down-regulation of bcl-2. The authors conclude that "[T]hese results suggest a role for autocrine and paracrine growth factors in the pathogenesis of B-CLL, and indicate that cytokines which prevent apoptosis in vitro may be targets for treating this malignancy" (Abstract). Further, the authors conclude, "[T]hese cytokines may act by preserving the expression of bcl-2 and suppressing apoptosis. The ability to interrupt cytokine networks in vivo may be exploited to augment existing therapies of B-CLL." (page 134).

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

In the instant case, the prior art discloses that PDE Type IV inhibition is useful in the treatment of diseases associated with excessive or unregulated production of cytokines or diseases which are associated with elevated cAMP levels or PDE-IV function in a particular target tissue. Further, it was known in the art that cytokines suppress the apoptosis of B-CLL cells. Thus, the prior art provides a nexus between PDE Type IV inhibition (which would lead to a decrease in cytokine production) and B-CLL (wherein cytokines suppress apoptosis of B-CLL cells).

The prior art did not recognize, at the time of the invention, that PDE Type IV was a molecular target in CLL. However, as noted *supra*, the nexus between PDE Type IV inhibition, cytokines, and CLL was established in the prior art.

Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to administer a specific PDE Type IV inhibitor to a patient having symptoms of CLL. The '754 patent explicitly contemplates the treatment of inflammatory diseases, diseases associated with excessive or unregulated production of cytokines and diseases which are associated with elevated cAMP levels or PDE-IV function. Tangye *et al.* disclose that human cytokines suppress apoptosis of leukemic B cells and preserve expression of bcl-2. As such, the skilled artisan would have been highly motivated to administer a specific PDE-IV inhibitor to a patient having symptoms of CLL. Said artisan would have been imbued with at least a reasonable expectation that a PDE-IV inhibitor would lead to a reduction in cytokines which would subsequently lead to increased apoptosis of CLL cells.

Allowable Subject Matter

Claim 15 is allowable over the prior art of record.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James D. Anderson whose telephone number is 571-272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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Patent Examiner
AU 1614

Phyllis Spivack

January 25, 2007

PHYLLIS SPIVACK
PRIMARY EXAMINER